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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/567,872 | 05/19/2006 | Ilia Fishbein | RCHP-135US | 1203 |

23122 7590 11/23/2009

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| EXAMINER | |
|---|---|
| SHEN, WU CHENG WINSTON | |
| ART UNIT | PAPER NUMBER |
| 1632 | |
| MAIL DATE | DELIVERY MODE |
| 11/23/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/567,872 | FISHBEIN ET AL. | |
| | Examiner | Art Unit | |
| | WU-CHENG Winston SHEN | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,8-10,17-28 and 34-37* is/are pending in the application.

4a) Of the above claim(s) *17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,8-10 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claim amendments filed on 08/11/2009 have been received and entered.

Claims 2, 4-7, 11-16, 29-33, and 38-40 are cancelled. Claims 1, 3, 8-10, 17-28, and 34-37 are pending. Claims 1, 3, 34, and 35 have been amended.

Claims 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3, 8-10, and 34-37 are currently under examination.

This application 10/567,872 is a 371 of PCT/US04/26509 filed on 08/13/2004, which claims benefit of 60/494,886 filed on 08/13/2003.

### *Claim Rejection - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Previous rejection of claims 1, 3, 8-10 under 35 U.S.C. 102(e) and 102(a) as being anticipated by **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008), is ***withdrawn***

because the claims have been amended. Previous rejection of claims 33, 39, and 40 are ***moot*** because claims 33, 39, and 40 have been cancelled.

Amended claim 1 filed on 08/11/2009 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker.

Levy et al. does not explicitly teach the amended limitation "wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein".

2. Previous rejection of claims 1 and 8-10 under 35 U.S.C. 102(e) as being anticipated by Kutryk et al. (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001), is ***withdrawn*** because the claims have been amended. Previous rejection of claims 33 and 39 are ***moot*** because claims 33 and 39 have been cancelled.

Amended claim 1 filed on 08/11/2009 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker.

Kutryk et al. does not explicitly teach the amended limitation "a composition comprising a metal surface chemically coordinated to a surface modifier".

***Claim Rejection - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Previous rejection of claims 1, 3, and 34 under 35 U.S.C. 103(a) as being unpatentable over **Kutryk et al.** (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001) in view of **Xu et al.** (US patent 7,001,745, issued date 02/21/2006, filed on 09/30/1999), is ***withdrawn*** because the claims have been amended. Previous rejection of claims 33 is ***moot*** because claim 33 has been cancelled.

Amended claim 1 filed on 08/11/2009 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker.

Neither Kutryk et al. nor Xu et al. explicitly teaches the amended limitation "a composition comprising a metal surface chemically coordinated to a surface modifier".

4. Previous rejection of claims 1 and 35-37 under 35 U.S.C. 103(a) as being unpatentable over **Kutryk et al.** (U.S. patent No. 7,037,332, issued May 2, 2006, filed on 03/15/2001) in view of **Li et al.** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000), is ***withdrawn***

because the claims have been amended. Previous rejection of claims 33 is ***moot*** because claim 33 has been cancelled.

Amended claim 1 filed on 08/11/2009 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker.

Neither Kutryk et al. nor Li et al. explicitly teaches the amended limitation "a composition comprising a metal surface chemically coordinated to a surface modifier".

*The following rejections under 35 U.S.C. 103(a) are necessitated by claim amendments filed on 08/11/2009.*

5. Claims 1, 3, 8-10, and 35-37 under 35 U.S.C. 103(a) as being unpatentable over **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008) in view of **Li** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000). *This rejection* is *necessitated by claim amendments filed on 08/11/2009.*

Amended claim 1 filed on 08/11/2009 reads as follows: A composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker.

Claim 3 further limits claim 1 by the limitation wherein the modified protein is covalently bound to the surface modifier through a thio residue and a linker. Claim 8 further limits the metal surface being a surface of a medical device. Claim 9 further limits claim 8 to medical device selected from the group consisting of a stent, a heart valve, a wire suture, a joint replacement, a urinary dilator, an orthopedic dilator, a catheter and an endotracheal tube. Claim 10 further limits claim 8 to the medical device being at least one of an internal device and an external device. Claim 35 further limits claim 1 by the limitation wherein the modified protein is a fusion protein and the fusion protein comprises a fragment of a CAR protein and a receptor targeting ligand. Claim 36 further limits claim 35 by the limitation wherein the fragment of the CAR protein is an extracellular domain of CAR or an immunoglobulin D1 domain of CAR. Claim 37 further limits claim 35 by the limitation wherein the receptor targeting ligand is selected from the group consisting of apolipoprotein E, transferrin, a vascular endothelial growth factor, a transforming growth factor-beta, a fibroblast growth factor, an RGD containing peptide, and folic acid.

With regard to limitations of claims 1 and 8, **Levy et al.** teaches a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated. Preferably, the surface modifier is an aminobisphosphonate. Levy et al. teaches that, still preferred, the surface modifier is a polyamine, and in another aspect of the invention, the composition further comprises a biologically active molecule. Levy et al. teaches that in another preferred embodiment, the biologically active molecule is an antibody which specifically binds a nucleic acid; and also preferred the nucleic acid comprises a vector system. Levy et al. teaches that in yet another aspect of the invention, the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], Levy et al., 2003/0044408, 2003). Levy teaches that a therapeutic delivery system efficiently introduces

biologically active molecules to mammalian cells without the use of synthetic polymers or biopolymer coatings. Surface modification of a metal support, such as stainless steel and titanium medical devices, a stainless steel stent, results in a single molecular layer that can fasten various molecules, thereby minimizing any cellular inflammatory response while enhancing biocompatibility (See abstract, and paragraph [0003] and [0010] Levy et al., 2003). Levy et al. teaches that the paired component which is most suitable for attachment to the surface-modified metal would be immobilized. The component is covalently cross-linked to a monomeric or polymeric surface modifier, which, in turn, provides chemical moieties that bind to the metal surface (See abstract, and paragraph [0026] and [0037], Levy et al., 2003).

With regard to the limitation "wherein the modified protein is covalently bound to the surface modifier through thiol residue and a linker" recited in claim 3, Levy teaches that in Fig. 2 depicts a reaction scheme for modifying surfaces of metal supports via amino group containing bisphosphonates. During an activation step, the N-succinimidyl ester group in SPDP (N-succinimidyl-3-(2-pyridyl- dithio)-propionate) reacts with the amino group of a chemosorbed polyamino-bisphosphonic acid, to activate a steel surface with a pyridyldithio group, and during a modification step, a thiol modified antibody is chemically linked to the metal (See paragraph [0013], US 2003/0044408. Levy et al, 2003).

With regard to the limitation of medical devices recited in claim 9 and the limitation of internal device and external device recited in claim 10, Levy et al. teaches that medical devices may include non-orthopedic devices, temporary placements and permanent implants, such as tracheostomy devices, intraurethral and other genitourinary implants, stylets, dilators, stents, vascular clips and filters, pacemakers [which reads on internal device], wire guides and access

ports of subcutaneously implanted vascular catheters [which reads on external device]. (See paragraph [0036], US 2003/0044408. Levy et al, 2003).

Related to the limitation "wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein" recited in claim 1, the limitation "wherein the modified protein is a fusion protein and the fusion protein comprises fragment of a CAR protein and a receptor targeting ligand" recited in claim 35, the fragment/domain of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37 "wherein the modified protein comprises a fusion protein or a polypeptide" recited in claim 33, Levy et al. teaches the composition comprises a biologically active molecule. Levy et al. teaches that in another aspect of the invention, the biologically active molecule is preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor (See paragraph [0008], US 2003/0044408. Levy et al, 2003).

However, Levy does not explicitly teach the limitation "wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein" recited in claim 1, the limitation "wherein the modified protein is a fusion protein and the fusion protein comprises fragment of a CAR protein and a receptor targeting ligand" recited in claim 35, the fragment/domain of the CAR protein recited in claim 36, and the receptor targeting ligand recited in claim 37.

Li teaches recombinant virus with a bispecific fusion protein ligand in coupling with an antibody to cell for gene therapy, and the fusion protein comprises extracellular domain of CAR/Hinge/protein A ligand, and Li develops a strategy using adenovirus as an example to

demonstrate the strategy of using the fusion protein to re-direct viral tropism (See title, abstract and Figure 1, Li). Li teaches that any extracellular domain of a viral receptor that is a membrane protein or membrane peptide can be used to replace extracellular domain of CAR and can be inserted as a part of the fusion protein ligand for targeting (See lines 20-24, column 8, Li). Li teaches that Arg-Gly-Asp (RGD) motif of viral pentose protein binds to integrins of cell membrane and this binding activates virus internalization via receptor-mediated endocytosis (lines 53-58, column 1, Li)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Levy et al. regarding a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, the biologically active molecule being an antibody, and also preferred, the biologically active molecule being preferably one component of an affinity pairing system, and still preferred, the biologically active molecule is avidin or biotin; IgG or protein A; or transferrin or its receptor, with the teaching of Li regarding fusion protein comprises extracellular domain of CAR/receptor targeting ligand, to arrive at the claimed invention of claims 1, 3, 8-10, and 35-37.

One having ordinary skill in the art would have been motivated to combine the teachings of Levy et al. and Li et al. because the fusion protein taught by Li can target specifically the receptor of interest present on cell membrane in the context of using viral vector to deliver therapeutic agent via the metal surface of a medical device, for instance, a stent taught by Levy et al.

There would have been a reasonable expectation of success given (i) successful demonstration of a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, and virus tethering stainless steel and in vivo cell transduction (See Example 5 of Levy et al.), by the teachings of Levy et al., and (ii) successful construction of the fusion protein comprises extracellular domain of CAR/receptor targeting ligand, by the teachings of Li.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

6. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Levy et al.** (U.S. 2003/0044408, publication date, 03/06/2003, filed on 06/14/2000; this reference is cited in the IDS filed by Applicant on 08/20/2008) in view of **Li** (US patent 6,524,572, issued date 02/25/2003, filed on 09/26/2000), as applied to claims 1, 3, 8-10, and 35-37 above, and further in view of **Xu et al.** (US patent 7,001,745, issued date 02/21/2006, filed on 09/30/1999).

The teachings Levy et al. and Li et al. have been discussed in the preceding section of the rejection of claims 1, 3, 8-10, and 35-37 under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Li.

None of Levy et al. and Li teaches the limitation the limitation "wherein the modified protein is a fusion protein and the fusion protein is generated through intein-mediated protein ligation" recited in claim 34.

Xu et al. teaches intein mediated peptide ligation to generate a fusion protein of interest and a method for producing a semi-synthetic fusion protein *in vitro*, comprising the steps of producing a target protein fused to a protein splicing element (an intein) and selectively cleaving

the fusion and ligating a synthetic protein or peptide at the C-terminal thioester of the target protein (See title and summary of invention, column 1, Xu et al.)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teaching of Xu et al. regarding generation of fusion protein of interest through intein-mediated protein ligation, into the combined teachings of Levy et al. and Li directed to a composition comprising a metal surface chemically coordinated to a surface modifier and a modified protein, wherein the modified protein comprises a fusion protein, or a CAR protein, or a fragment of a CAR protein, and wherein the modified protein is covalently bound to the surface modifier directly or via a linker, to arrive at the claimed invention of claim 34.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Xu et al. into the combined teachings of Levy et al. and Li because the intein-mediated protein ligation taught by Xu et al. provide a high-yield, semi-synthetic technique to allow *in vitro* fusion of a synthetic protein or peptide fragment to an expressed protein without limitation as to the size of the fused fragments.

There would have been a reasonable expectation of success given (i) successful demonstration of a composition comprising a surface modifier and a metal support to which said surface modifier is chemically coordinated, and the composition further comprises a biologically active molecule, and virus tethering stainless steel and in vivo cell transduction (See Example 5 of Levy et al.), by the teachings of Levy et al., and (ii) successful construction of the fusion protein comprises extracellular domain of CAR/receptor targeting ligand, by the teachings of Li, and (iii) successful demonstration of direct ligation of a peptide to the thioester formed between

VMA intein and maltose binding protein, by the teachings of Xu et al. (See Figure 3, lines 48-50, column 2, Xu et al.)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

***Applicant's arguments and Response to Applicant's arguments***

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. It is noted that previous 102 and 103 rejections documented in the non-Final office action mailed on 05/27/2009 have been withdrawn. In this Final office action claims 1, 3, 8-10, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Li; and claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. in view of Li, as applied to claims 1, 3, 8-10, and 35-37 above, and further in view of Xu et al.

***Conclusion***

7. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632